Preinvasive Lesions of the Bronchus

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Abstract: Preinvasive lesions are considered the precursors of squamous cell carcinoma of the bronchus. Treatment at the preinvasive stage, before the potential for metastasis, may improve survival from squamous cell carcinoma. An understanding of the natural history and outcome of preinvasive lesions is essential for the accurate interpretation studies of their treatment, and decisions regarding the management of individual lesions. The natural history of preinvasive lesions has only been reported in a small number of highly selected patients and uses different inclusion criteria, treatment criteria. and time-periods of follow-up, making it difficult to draw definitive conclusions. High-grade preinvasive lesions carry a risk of progression to carcinoma but most patients have multiple lesions and a significant probability of developing new lesions over time. Distinguishing lesions with malignant potential, the targets for therapy, from those that will regress or remain indolent is difficult. The American College of Chest Physicians guidelines recommend bronchoscopic follow-up of severe dysplasia and carcinoma-in situ. This review of the evidence regarding the natural history and outcome of preinvasive lesions supports this view, but also shows that further studies in individuals at risk for lung cancer are necessary before guidelines for the management of preinvasive lesions can be developed.

Key Words: Preinvasive lesions, Bronchial carcinoma, Natural history.

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Preinvasive lesions are defined as "a precursor lesion of squamous cell carcinoma arising in the bronchial epithelium. Squamous dysplasia and carcinoma-in situ are a continuum of recognisable histologic changes in the large airways. They can occur as single or multifocal lesions throughout the tracheobronchial tree. Dysplasia or carcinoma-in situ may exist as an isolated finding or as a bronchial surface lesion accompanying invasive carcinoma."[1] They are small, and difficult to visualize using conventional white light bronchoscopy.[2] Autofluorescence bronchoscopy has been developed specifically to detect preinvasive lesions, and has improved the sensitivity of lesion detection by 1.5 to 6 fold.[3–5] The ability to detect lesions, particularly those of higher-grade, has enabled the study of preinvasive lesions as a means of early identification and treatment of squamous cell carcinoma of the bronchus.

The basement membrane is intact[6] in preinvasive lesions, and there is no possibility of metastatic spread, which is in contrast to squamous cell carcinoma where there is the potential for metastasis as soon as invasion occurs. There is some evidence that a 90% 5-year survival might be achieved by treating lesions at the preinvasive stage.[7,8] Consequently, preinvasive lesions are thought good candidates for therapy, with the aspiration that their treatment will improve long-term survival from carcinoma of the bronchus. There is a discrepancy between the prevalence of preinvasive lesions[9] and the incidence of lung cancer,[10] which suggests that not all lesions inevitably develop into carcinoma. This raises questions regarding their treatment, as lesions that are not at risk for malignancy should not require intervention. To determine which lesions are at risk, a knowledge of the natural history of preinvasive lesions is necessary.

The entire bronchial epithelium is exposed to carcinogen from cigarette smoke, and malignancy can develop in any location within that exposed epithelium.[9,11] It has been suggested that the only way to treat this "field carcinogenesis" is to use a systemic chemopreventative agent. Although one trial showed some benefit,[12] others have been less successful.[13–15] As our understanding of the biology of preinvasive lesions and the genetic switches that control their behavior increases, it is anticipated that specific chemopreventive agents will be discovered. However, the outcomes of studies of chemopreventative agents cannot be accurately assessed until a reliable predictive model for the long-term progress of individual preinvasive lesions is available. An understanding of the natural history of preinvasive lesions is central to both the interpretation of studies of treatment, and also decisions regarding the management of manifest lesions.

Prevalence of Preinvasive Lesions

The seminal study by Auerbach et al.[9] in the 1950s showed that preinvasive lesions were a frequent finding in the bronchial epithelium of smokers and patients with lung cancer. Only male patients were included, and the study was performed on a very different population from the patients of today. There was no "dysplasia" category in their classification of lesions, and carcinoma-in situ was defined as "all bronchial epithelial lesions composed entirely of atypical cells and lacking cilia." The authors accepted that there were

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differences between the lesions categorised as "carcinoma-in situ" but could not differentiate the lesions further due to a lack of sensitivity in their techniques. Furthermore, the nature of cigarettes and smoking has changed over the last 50 years.[16] For these reasons the prevalence data for preinvasive lesions from 50 years ago may not be applied easily to today's patients.

The prevalence of preinvasive lesions was addressed in a more recent study by Paris et al.[17] In 241 patients at high risk for lung cancer (as defined by the International Association for the Study of Lung Cancer criteria) the prevalence of high-grade preinvasive lesions was 9%. The prevalence was higher in current (12%) than former smokers (4%). The severity of dysplasia observed within the bronchial tree was related to the extent of tobacco exposure. There was a clear association between the presence of high-grade preinvasive lesions and previous carcinoma of the bronchus, a history of head and neck carcinoma (odds ratio 4.0 based on 15 patients) and occupational exposure to asbestos or other carcinogens. The risk of having a high-grade preinvasive lesion ranged from 0.2 to 90.4% and was related to the number of risk factors for carcinoma within the individual patient. A multicenter randomized study by Häußinger et al.[18] using a different autofluorescence system stratified 1173 patients by their risk factors. The highest prevalence of preinvasive lesions was in patients with abnormal sputum cytology but normal chest radiology (11.1%). Patients with previously resected carcinomas had a prevalence of 6.7% and those with radiologic or clinical suspicion of lung cancer 4.6%. There were no preinvasive lesions found in those with Chronic Obstructive Pulmonary Disease or occupational exposure to carcinogen alone.

Further data are available from the chemoprevention studies of Lam and colleagues where volunteer smokers underwent autofluorescence bronchoscopy. The prevalence of carcinoma-in situ was 1.8%, severe dysplasia 6.5%, moderate dysplasia 14%, and mild dysplasia 40%.[19] Males seemed to have a higher prevalence of preinvasive lesions, high-grade lesions occurring in 31% of males but only 14% of females.[19] The overall prevalence and number of lesions per patient were lower in females even after adjustment for smoking. The reasons for this are not clear but may be related to sex-related differences in the susceptibility of the epithelium to the toxic effects of cigarette smoke.

Implications of the Presence of Preinvasive Lesions

The presence of preinvasive lesions of the bronchus signifies an increased likelihood of development of carcinoma of the bronchus. Loewen et al.[20] recently described a group of 169 patients from the USA undergoing surveillance using computed tomography scanning and autofluorescence bronchoscopy. Of the patient group, 66% had preinvasive lesions of squamous metaplasia or worse and 7% developed a lung cancer in the 3 to 16 month follow-up period, over half of which were adenocarcinomas. A similar group of 46 patients, reported by Pasic et al.,[21] were followed up using autofluorescence bronchoscopy 4 to 6 monthly for a median of 50 months. The number of preinvasive lesions found within the airways was related to the patient's probability of carcinoma development. In contrast to the USA study above, 24% of this Dutch group of patients developed squamous cell carcinoma; no adenocarcinomas were found. The relationship between the individual lesions followed and the development of carcinoma was not discussed. A 4 year study in Italy[22] showed that 10 of 22 patients with dysplasia developed a carcinoma, 7 of which were squamous cell, during follow-up. The grade of dysplasia at baseline was related to the probability that a carcinoma would occur. There was no bronchoscopic follow-up, and so once again the relationship between individual lesions and the development of carcinoma could not be determined. Additional information is provided by the study by Sin et al.[23] from Canada, where a raised serum C-reactive protein was associated with the histologic progression of dysplasia or the development of new lesions in 50% of the study patients. These data suggest that in patients at high-risk for lung cancer, preinvasive lesions of high grade are prevalent. The risk of development of carcinoma of the bronchus, particularly squamous cell, is related to their number and severity.

Natural History of Preinvasive Lesions

The literature on the subject has accumulated over 50 years and is difficult to interpret. The criteria for the diagnosis and classification of preinvasive lesions has changed twice[1,6,9,24] which makes the analysis of older studies problematic. The possibility that an individual lesion may progress to an invasive carcinoma has prompted some groups to take the view that all carcinoma-in situ should be treated.[25] Thus in many studies carcinoma-in situ and invasive carcinoma were joint end-points, which compromises evaluation of the natural history of high-grade lesions.[26,27] In most studies, higher grade lesions have been followed up for only very short periods of time, typically less than 6 months, and usually not as far as the development of invasive malignancy.[25] The lesions were then treated, which invalidates the follow-up data.

Despite the 2004 World Health Organization guidelines,[1] the differentiation between severe dysplasia and carcinoma-in situ, particularly in biopsy specimens, can be difficult. It is interesting to note that the agreement between the two observers for the reporting of the histopathology has not been stated in any of the studies, nor was the quality of the biopsies assessed. This is despite known difficulties with the subdivision between mild and moderate dysplasia, between severe dysplasia and carcinoma-in situ, and also the effect of the quality and structural integrity of the biopsy on the interpretability of the histologic features.[28] Bronchoscopic biopsy and specimen processing is known to compromise the histologic appearance of some specimens. The interpretation of studies of the natural history of preinvasive lesions is critically dependent on accurate histology, particularly if differentiation is to be made between carcinoma-in situ and severe dysplasia. Assessment of interobserver agreement and the quality of the biopsies presented should be an important first step in the analysis of preinvasive lesion histologic follow-up data.

All of the studies of the natural history of preinvasive lesions have used biopsy and histopathology to determine the histologic grade of the lesions under follow-up. However, biopsy involves disruption and removal of a proportion of the lesion. The effect of this disruption and the impact on the natural history of the lesion under investigation is not known. Additionally, preinvasive lesions are often small,[2] and may be completely removed during biopsy.[25] This suggests that the results of previous studies of the natural history of preinvasive lesions may have been compromised by biopsy. The effect of biopsy will not be known until accurate and reproducible methods of lesion classification using noninvasive means are developed.

TABLE 1. Studies of Follow-Up of Preinvasive Lesions

Study	Selection Criteria	Patients (*n*)	Male (%)	Lesions (no.)	Follow-up (mo)	Lesion Types Included	Lesions Types Excluded	Comments
Lam 2001[12]	High-risk	101	61	248	6	Up to severe dysplasia	CIS and carcinoma	Chemoprevention study
Bota 2001[25]	High-risk	104	96	416	3–24	Up to SD	CIS treated	
Jeanmart 2003[27]	Ex-smokers	48	94	80	18–36	Up to SD	CIS and carcinoma end-points	
Breuer 2005[26]	Smokers	52	85	134	11–21	Up to SD	CIS and carcinoma end-points	
Hoshino 2004[29]	Detected lesions	50	98	99	6–17	Up to SD	None	
Moro-Sibolot 2004[30]	Detected lesions	27	89	31	25	CIS and SD	LGL and carcinoma	
Lamy 2002[32]	Detected lesions	37	NA	29	19–28	All	No SD/CIS reported	Methylation status and outcome
Sozzi 2002[31]	Detected lesions	2	100	20	48	All	CIS treated	Case study two patients
Keith 2000[42]	ASD only	11	NA	20	12	ASD	All others	Part of larger histology study
George 2007[33]	High risk	22	86	36	12–85	All	None	9 patients previous cancers
Lam 2002[12]	High risk	91	61	245	6	All	None	Chemoprevention study
Lam 2004[14]	High risk	112	73	403	6	All	None	Chemoprevention study
Studies Performed Using Pre-1999 WHO Criteria for Pre-invasive Lesions								
Satoh 1997[34]	SD and MiD only	3	100	4	7–72	3 SD and 1 MiD	None	Lesion follow-up case study
Venmans 2000[36]	CIS only	9	78	13	6 mo	CIS + detected in follow-up	All others	PDT treatment study
Thiberville 1995[35]	High-risk	6	92	11	48	All	Some CIS treated	Molecular changes study
Studies in Which Lesions Were Treated								
Deygas 2001[40]	CIS only	35	97	41	1–12	CIS	All others	Study of cryotherapy
Studies of Resection Margin CIS								
Pasic 2005[43]	CIS only	11	82	11	11–89	CIS resection margin	All others	Resection margin lesions only

Studies in Which Patient Outcome Determined (no individual lesion data)

Study	Selection Criteria	Patients (no.)	Male (%)	Follow-up (mo)	Outcome	Purpose of Study
Sin 2006[23]	"Dysplasia"	65	75	6	50% progression at 6 mo	Relationship outcome to CRP
Ponticiello 2000[22]	High-risk with dysplasia	22	69	48	10/22 carcinoma	Relationship outcome to grade of dysplasia and p53
Pasic 2003[21]	High-risk	46	85	12–80	11/46 carcinoma	Retrospective. Relationship number of lesions to outcome

High-risk is as defined by the IASLC criteria.

MiD, Mild dysplasia; MoD, Moderate dysplasia; SD, Severe dysplasia; CIS, Carcinoma-in-situ; ASD, Angiogenic squamous dysplasia; LGL, Low-grade lesion; PDT, Photodynamic therapy; CRP, C-reactive protein; IASLC, International Association for the Study of Lung Cancer.

The studies in which follow-up data on preinvasive lesions can be found are listed in Table 1. Given the difficulty in detecting preinvasive lesions,[2] and their relatively low frequency in the at-risk population,[18] it is not surprising that the majority of studies have included patients in whom preinvasive lesions have already been identified. Most have followed individual lesions, but some have followed the whole patient, reporting outcome in terms of the observed carcinoma, regardless of it's location or cell type. There is heterogeneity between the groups of patients included, the specific types of lesion followed, the end-points of the studies and the criteria for intervention for preinvasive lesions.

The largest study, that of Bota et al.,[25] followed carcinoma-in situ for only 3 months before endobronchial therapy. No further posttreatment data are given, and the efficacy of the treatments applied are not evaluated. Severe dysplasia was followed up, and found to regress in a significant proportion of patients. Only the ultimate outcome of an individual lesion was reported, limited by the length of the study, and not the specific histologic or bronchoscopic features as they evolved over time. Jeanmart et al.[27] reported the outcome of individual lesions over time. As both carcinoma-in situ and invasive carcinoma were end-points the outcome of severe dysplasia and carcinoma-in situ are difficult to evaluate with certainty. The study by Breuer et al.[26] had similar issues, with the definition of "progression" of a high-grade lesion including lesions that had remained stable for 3 months, or progression from severe dysplasia to carcinoma-in situ. Only 11 lesions of high-grade were identified in the study by Hoshino et al.[29] and no lesions of carcinoma-in situ, while studies by Moro-Sibolot et al.,[30] Sozzi et al.,[31] and Lamy et al.[32] contribute very few high-grade lesions to the literature. George et al.[33] reported 22 carefully characterized patients followed for a median of 23 months. Although this group was highly selected, the results were not compromised by treatment to lesions. The lesions were grouped into "high-grade" and "low-grade" categories to minimize the risk of observer error in the histopathological reporting of bronchial biopsies. The placebo arms of the chemoprevention studies of Lam et al. provide valuable information, although follow-up was for only 6 months and there were very few high-grade lesions.[14,15]

It is difficult to interpret the studies of Satoh et al.,[34] Thiberville et al.,[35] and Venmans et al.[36] alongside the more recent studies as the lesions were classified using the 1981 World Health Organization criteria.[24] In the study by Venmans et al.[36] in particular, all the carcinoma-in situ was treated, which compromised the results. Satoh et al.[34] followed 4 lesions in 3 patients, all of which developed into invasive carcinoma in up to 6 years. It is conspicuous that the high grade lesions progressed more rapidly than the low-grade lesion. The study by Thiberville et al.[35] followed the histologic and molecular progression of a series of preinvasive lesions, some of which were treated and some of which were not. Four lesions are shown with their detailed histologic follow-up data in the study by Breuer et al.,[26] but without timescales. These two studies also demonstrate that there is some biopsy to biopsy variation of the histopathological diagnosis of lesions under follow-up.

Tables 2, 3 show the outcome of preinvasive lesions from the literature. When the data from all the studies are combined it is noted that preinvasive lesions may progress to invasive squamous cell carcinoma, and the risk is much higher for high-grade lesions than low-grade lesions. The probability of progression seems higher for carcinoma-in situ than severe dysplasia, but this is based on the analysis of 49 carcinoma-in situ lesions. It is not clear whether carcinoma-in situ had indeed progressed to invasive carcinoma or persisted as carcinoma-in situ in many of these lesions which makes interpretation of the data difficult. A significant proportion of carcinoma-in situ and severe dysplasia lesions regress towards normal epithelium. It has been suggested that severe dysplasia is more likely to regress than carcinoma-in situ, but the protocol of the study in question treated carcinoma-in situ if it persisted at 3 months which invalidates the conclusions drawn.[25] It is observed that as many carcinoma-in situ lesions remain stable as progress to invasive carcinoma or regress towards normal, suggesting that the length of follow-up has been inadequate for some of these lesions. Combining carcinoma-in situ and severe dysplasia together into a "high-grade" lesion category shows an equal rate of progression and regression. Low-grade lesions have a comparatively low risk of progression and are most likely to regress to normal or remain stable.

These data are based on 165 high-grade lesions in the literature. It is questionable, given the low numbers of lesions followed-up and the heterogeneity of inclusion criteria and reporting of outcomes, whether any firm conclusions regarding the clinical management of high-grade preinvasive lesions can be drawn. There are no clinical features that predict the outcome of a manifest lesion. In this context, it would be important to balance the risk of progression against the efficacy of treatment, and the risk of significant disease elsewhere in the bronchial tree.

All of this information must be interpreted in the light of the changing histology of lung cancer worldwide. The incidence of adenocarcinoma is increasing in some countries, but squamous cell carcinoma remains the most frequent histologic type in others.[37,38] In one study, preinvasive lesions were associated with the presence of peripheral nodules within the lung.[20] It is possible that the relevance of preinvasive lesions in terms of the risk of carcinoma development may be changing. Alternatively, preinvasive lesions could simply be a marker of cigarette exposure sufficient to induce carcinogenesis but further detailed study is required.

Endobronchial Therapy and Preinvasive Lesions

It has been suggested that endobronchial therapies may be effective in treating high-grade lesions while sparing lung and therefore lung function.[39,40] Review of studies in which lesions were treated and individual lesion follow-up data are given (Table 3) shows that over one third of treated carcinoma-in situ progresses to invasive carcinoma, regardless of the treatment modality used (although the most frequently used is Photodynamic therapy). Interestingly, the proportion of le-

TABLE 2. Studies of Follow-Up of Untreated Preinvasive Lesions

	Bota 2001[25]	George 2007[33]	Jeanmart 2003[27]	Breuer 2005[26]	Hoshino 2004[29]	Moro-S 2004[30]	Lamy 2002[32]	Satoh 1997[34]	Thiberville 1995[35]	Lam 2004[14]	Lam 2003[15]	Total (numbers)	Total (%)
CIS progression	0–25/32	X	5/8	X	X	2/7	X	X	1/2	X	X	8–33/49	16–67
CIS regression	7/32	X	0/8	X	X	3/7	X	X	0/2	X	X	10/49	20
CIS stable	0–25/32	X	3/8	X	X	2/7	X	X	1/2	X	X	6–31/49	12–63
SD progression	0–8/27	X	2/9 SQC 4/9 CIS	8/25 incl CIS	2/11 SQC	1/1	X	3/3	X	0/2	0/2	20–28/80	25–35
SD regression	19/27	X	3/9	13/25	5/11	0/1	X	0/3	X	2/2	2/2	44/80	55
SD stable	0–8/27	X	0/9	4/25	4/11	0/1	X	0/3	X	0/2	0/2	8–16/80	10–20
HGL progression	0–33/59	6/36	7/17	8/25 incl some stable	2/11	3/8	X	3/3	1/2	0/2	0/2	30–63/165	19–38
HGL regression	26/59	7/36	3/17	13/25 excl CIS	5/11	3/8	X	0/3	0/2	2/2	2/2	61/165	37
HGL stable	0–33/59	23/36	7/17	4/25 excl CIS	4/11	2/8	X	0/3	1/2	0/2	0/2	41–74/165	25–45
LGL progression	6/169	0/17	11/18	9/64	1/88	X	6/29 HGL/SQC	1/1	0/9	0/145	3/105	37/645	6
LGL regression	100/169	14/17	7/18	41/64	50/88	X	0/29	0/1	3/9	102/145	61/105	378/645	59
LGL stable	63/169	3/17	0/18	14/64	37/88	X	23/29	0/1	6/9	43/145	41/105	230/645	36
MPA progression	48/152	X	5/26	13/45	X	X	X	X	X	12/68	16/29	94/320	29
MPA regression	56/152	X	0–21/26	19/45	X	X	X	X	X	0/68	8/29	83–104/320	26–32
MPA stable	48/152	X	0–21/26	13/45	X	X	X	X	X	56/68	5/29	122–143/320	38–45
Distant carcinoma (number)		5	3/8				6						
Duration of follow-up (mo)	3–24	12–85	18–36	11–21	6–17	25	19–28	7–72	48	6	6		

The numbers of lesions with the given outcome are shown for each study.
A range is given for studies where differentiation between outcomes cannot be determined from the data, e.g. carcinoma-in-situ stable at 3 mo or progression to invasive carcinoma.
The outcomes of the lesions are therefore calculated as a range.
MPA, metaplasia; LGL, low-grade lesion; HGL, high-grade lesion; SD, severe dysplasia; CIS, carcinoma-in-situ.

TABLE 3. Studies of Follow-Up of Treated Preinvasive Lesions

	Venmans 2000[36]	Lam 2002[12]	Deygas 2001[40]	Moro-Sibolot 2004[30]	Sozzi 2002[31]	Lam 2003[15]	Lam 2004[14]	Total (no. patients)	Total (%)
Distant SQC			8/35						
CIS progression	2/6	X	7/35	11/21	2/2	X		22/64	34
CIS regression	3/6	X	25/35	9/21	0/2	X		37/64	58
CIS stable	1/6	X	3/35	1/21	0/2	X		5/64	8
SD progression	3/3	X	X	1/2	0/1	0/2	0/2	4/10	40
SD regression	0/3	X	X	1/2	1/1	2/2	2/2	6/10	60
SD stable	0/3	X	X	0/2	0/1	0/2	0/2	0/10	0
HGL progression	5/9	X	7/35	3/8	2/3	0/2	0/2	17/59	29
HGL regression	3/9	X	25/35	3/8	1/3	2/2	2/2	36/59	61
HGL stable	1/9	X	3/35	2/8	0/3	0/2	0/2	6/59	10
LGL progression	1/4	1/94	X	X	1/2	3/108	3/114	9/322	3
LGL regression	3/4	55/94	X	X	1/2	74/108	73/114	206/322	64
LGL stable	0/4	38/94	X	X	0/2	31/108	38/114	107/322	33
MPA progression	X	8/20	X	X	X	5/23	15/56	28/99	28
MPA regression	X	10/20	X	X	X	10/23	34/56	54/99	54
MPA stable	X	2/20	X	X	X	8/23	7/56	17/99	17
Treatments	PDT	CP	Cryotherapy	Various endobronchial	Specific chosen	CP	CP		

The numbers of lesions with the given outcome are shown for each study.
MPA, metaplasia; LGL, low-grade lesion; HGL, high-grade lesion; SD, severe dysplasia; CIS, carcinoma-in-situ; PDT, photodynamic therapy; CP, chemoprevention.

sions progressing is similar to that of untreated carcinoma-in situ. The numbers of lesions of severe dysplasia treated are too small to draw valid conclusions. Low-grade lesions appear to derive no benefit from endobronchial therapy, with the results of post-treatment follow-up almost identical to that of untreated lesions. In addition, there is an observed incidence (up to 37%) of the development of carcinoma elsewhere in the lungs from 3 studies.[27,33,40] For example, George et al.[33] showed a similar incidence of developing distant carcinoma to that of carcinoma within the high-grade preinvasive lesion of interest. These data suggest that local endobronchial treatment may be inadequate for the treatment of carcinoma-in situ, may not prevent progression to invasive carcinoma and cannot prevent distant carcinoma, although these conclusions are based on a small number of treated lesions. To date the only known effective therapy is surgery, which can only be performed a limited number of times, carries a significant morbidity, and may preclude curative treatment should a carcinoma arise elsewhere. This approach cannot be justified for an individual lesion when the risk of malignant transformation is not known. The caveat is that, these data were obtained before the widespread use of endobronchial ultrasound and optical coherence tomography. It is impossible to determine whether the treated lesions in the various studies were genuinely carcinoma-in situ or occult carcinoma, and whether the treated depth was adequate. Studies of endobronchial therapy guided by these newer techniques are necessary to re-establish their efficacy.

In Summary

The natural history or progress of preinvasive lesions of the bronchial epithelium over time has only been reported in a small number of highly selected patients. Such studies offer a short-term window onto the changing and evolving environment of the bronchial mucosa. The literature regarding the natural history of preinvasive lesions uses different inclusion criteria, treatment criteria and time-periods of follow-up, making it difficult to draw definitive conclusions using the available data in this context. Bronchial carcinogenesis is a long-term process which may take several years to develop, and may occur at any time-point and any location within the bronchial tree. There is no doubt that high-grade preinvasive lesions carry a risk of progression to carcinoma but most patients have multiple lesions and a significant probability of developing new lesions over time. Distinguishing lesions with malignant potential, the targets for therapy, from those that will regress or remain indolent is difficult. The American College of Chest Physicians guidelines[41] recommend bronchoscopic follow-up of severe dysplasia and carcinoma-in situ. Review of the evidence supports this view, but also shows that further studies of the natural history of preinvasive lesions in individuals at risk for lung cancer are necessary before guidelines for the management of preinvasive lesions can be developed.

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